safety aspect. That wasn't done here.

Okay.

MS. WOOD: Effectiveness: the primary effectiveness endpoint of the LACI II study was limb salvage, absence of major amputation, at six months. In the LACI II study, documented limb salvage at six months was achieved in 110 patients, 75.9 percent of 145 patients enrolled. Of the other 35 patients, 15 dies, 11 were lost to follow-up, and nine had major amputations. Two other major amputations were performed on patients who subsequently died.

By comparison, limb salvage at six months in the control group was achieved in 494 of the 673 patients, 73.4 percent. Of the other 179 patients, 96 died, seven were lost to follow-up, and 76 had amputations.

Rutherford Class 6 was the only significant univariate predictor for this effectiveness endpoint. Eleven, 7.5 percent, LACI patients were in this class at baseline. By comparison, 60, 7.6 percent, control patients were listed at enrollment as being in Fontaine Class V,

which includes both gangrenous ulceration and tissue loss.

Of the 110 LACI patients who were evaluated at six months and were free of major amputation, 43, 39 percent, continued to be classified with CLI. This is compared to 211, 43 percent, cases of persistent CLI in the control group reported by ICAI.

3. The clinical objectives of the study were states as:

(i) Protection from acute amputation;

(ii) limb salvage;

(iii) resolution of CLI; and

(iv) preservation of surgical options.

Please comment on whether the outcomes for the LACI study demonstrate that these objectives have been achieved.

CHAIRMAN LASKEY: Well, again, I'll let Gary speak to this. He was the lead reviewer and, I think, articulates the panel's sentiments.

DR. NICHOLAS: I'll just take it A through D.

Protection from acute amputation. Again, we are comparing to what we all agree is a very weak control population, but there's no difference.

Limb salvage. Exactly the same answer, I'm afraid.

Including the people that remain in the categories that we call critical limb ischemia seems to be the same in the control and the study population.

And I think the whole protocol here, if I can digress for just a moment, suffers from the control population. I think there is some merit here. I think it needs to be sorted out, and I think that this is a technology and a technique that many of our patients will be able to use who are in this desperate situation.

To come back to then number D, preserving surgical options. Yes, in the study group of 145 people they did demonstrate that there were two in whom they identified bypass vessels that were not previously present. We don't know the

follow-up on those two patients, and certainly it's too small to make any positive assertion about preservation of surgical options.

They did have a low incidence of distal embolization, which obviously is a very positive finding, but again, I think the study really didn't demonstrate that we saved surgical options.

CHAIRMAN LASKEY: So in summary, overall we have a safe measure, but no real convincing measure of efficacy. Is that a good way to sum --

DR. NICHOLAS: That's the way I look at it.

CHAIRMAN LASKEY: Because of the conversation we've had all day about compared to what. Okay.

MS. WOOD: Are you ready for the next one?

CHAIRMAN LASKEY: yes.

MS. WOOD: Laser ablation requires crossing of the culprit lesions with a guidewire for control of energy delivery. Where standard guidewire crossing cannot be achieved, "step-wise"

use of the laser can assist in achieving guidewire crossing.

In LACI, the guidewire negotiated the lesion without need of laser in all but 25/155, 16.7 percent, limbs. Following the use of laser energy, balloon angioplasty was required in all cases for the final reduction of lesion obstruction to less than 50 percent angiographically. This procedural success was attained in 132/155 limbs, 85 percent.

4. Please comment on the added value provided by the laser therapy, which is used as an adjunct prior to the PTA required for final resolution of the lesion obstruction.

CHAIRMAN LASKEY: So if you could rephrase the first third of your comments a few moments ago, I think that was germane to the adjunctive value of the laser here.

I'm not sure we all share your sentiment, but at least rephrase it for discussion.

DR. SOMBERG: Well, my feel, and I'm only going to say my feeling was that the current study did not demonstrate the adjunctive value. It

could be demonstrated in a number of potential study designs, one of which was being that it could be randomized to two groups receiving interventional therapy. One group only has the laser added as an adjunctive therapy. That was essentially what I said before.

I will also interject that within the database that this company has presented, there may be a small but finite group where they could demonstrate benefit because nothing could be done for those patients until the laser was used, although we did see some discussion of what was the approach. Did they put the guidewire in first? Did they use the laser first?

But that might be something that the agency and the company would discuss at a later date.

DR. FERGUSON: Warren, could I make a comment? Somebody else?

CHAIRMAN LASKEY: Go ahead, Tom.

DR. FERGUSON: No, I'm getting back to the point about using the word "adjunctive," and

again would stress from my point of view it is almost necessary to use both modalities, the laser and the balloon as a part of the treatment package, and I just bring that up again because, again, I don't see how the two can be separated, frankly.

I don't do this work, but --

CHAIRMAN LASKEY: Well, and this study is certainly not as near universal use of PTA. So there would have to be another design.

Anybody else?

DR. TRACY: Warren, I just had a thought. I completely do not think that we can understand the adjunct value of this thing because initially I thought that I think it was 13 percent that were crossed by laser that could not have been crossed by wire alone, but then it sounded like there was some different technique of laser-wire, laser-wire, laser-wire, laser-wire.

So I don't think there's data in here that can help us understand. I think it probably is an adjunct, but I don't think we can look at that.

DR. FERGUSON: My comment related to the

other end though.

CHAIRMAN LASKEY: Yeah, the other 98.

DR. FERGUSON: The other end being if you use only the laser I don't think you've done a complete, and they can correct me if that's wrong.

DR. KRUCOFF: Warren.

CHAIRMAN LASKEY: Mitch, yeah.

DR. KRUCOFF: Yeah, I mean, the way I would go would be to do your best to identify people in whom all of the angiographic, morphologic criteria suggest that getting a guidewire through the lesion or a balloon over that guidewire are simply not going to be doable, and in that population even just technical success with or without the laser as an adjunct could give you, I think, some very quick information that would support the ability to answer this question.

CHAIRMAN LASKEY: Another study.

Move on, yeah.

MS. WOOD: Risk-benefit: co-morbidity associated with CLI has accounted for mortality greater than 50 to 60 percent in patients out to

five years and as high as 40 percent at two years in some reports. Primary amputation has been recommended as an acceptable alternative to revascularization attempts in some cases.

While freedom from amputation was obtained in 110 of the 155 limbs in this study, 15 patients died and 43 patients remained in Rutherford classifications for CLI. In addition, rehospitalization for SAEs was necessary for 48, 36 percent, patients.

5. Please comment on whether the benefit demonstrated in this study, particularly, with respect to quality of life-years, outweighs the adverse events that occurred and the persistence of CLI documented.

CHAIRMAN LASKEY: Well, we gave the sponsor what I thought was a wide open opportunity to talk about quality of life, but he chose not to run with that. I was curious why.

I mean, we went after some of the other endpoints here in the study that are certainly important and should be in every study henceforth in

this kind of patient population. But I guess the panel did not discuss in depth the quality of life-years or the risk-benefit ratio, if you will.

We tried to get that from the sponsor, and we didn't get very far. That's my take-home message. It's there. I mean, you have it. I don't know why you didn't present it.

MS. WOOD: Moving on to labeling, six, labeling for a new device should indicate which patients are appropriate for treatment, identify potential device-related adverse events, and explain how the device should be used to optimize its risk-benefit profile.

If you recommend device approval please address the following:

(a) Do the indications for use, as stated below, adequately define the patient population and procedural use for which the device will be marketed?

"The Spectranetics CVX-300 Excimer Laser System is indicated for facilitation of limb salvage in patients with critical limb ischemia (associated

with Rutherford Categories 4, 5 and 6) who have angiographically evident culprit stenoses and/or occlusions in the SFA, popliteal and/or infrapopliteal arteries, who are poor surgical candidates, and who are acceptable candidates for revascularization."

CHAIRMAN LASKEY: Well, these are certainly the inclusion criteria, but I'm not sure we can go any further with that based on where we're hung up with respect to the efficacy of the device. So I'm not sure where else we can go with that.

DR. ZUCKERMAN: That's a fair response.

MS. WOOD: (b) Based on the study results, please discuss whether the proposed warnings, precautions, and contraindications are acceptable.

CHAIRMAN LASKEY: Again, with the same caveats, I don't think that these questions really are relevant in this particular --

DR. ZUCKERMAN: Well, I think there's a standard policy where we need to review the labeling regardless of what happens in the next section. For

example, I'm looking at Section 3 of your panel pack, which is the labeling, and under the contraindications section, for example, it is written "no known contraindications for laser."

We need generic type help here. Is that appropriate? Are there certain things in warnings and precautions for peripheral vascular device, such as the laser, that one would want to see in an FDA label?

DR. TRACY: I think from the standpoint of the warnings and precautions it looks inclusive of the types of things that you'd worry about generically with the use of a laser device. So I have no problem with what's stated here.

I think we just need a little bit more clinical information to know whether such statements as no known contraindications, whether that's appropriate. But I think this how to use a laser device, I think these are appropriate warnings and precautions.

CHAIRMAN LASKEY: Is it fair to say it should be consistent with your coronary indication,

or is there some reason to broach that?

DR. ZUCKERMAN: We can review that labeling, but, Dr. Nicholas, for example, would you have any special concerns that you would want to see in the labeling for a peripheral vascular device?

DR. NICHOLAS: No, I think the labeling and the indication as it's written is very well written and I would support that, given the efficacy issue.

MS. WOOD: (c) Please discuss whether the instructions for use adequately describe how the device should be used.

CHAIRMAN LASKEY: Well, here I don't think that it has been adequately described. There are nuances to the approach of these lesions. You can wire first; you can lase (phonetic) first; you can do a little of both. I think the IFU needs to be fairly specific if the company is intent on furthering this technology.

What we heard today were a number of non-protocol regulated approaches left to the discretion of the operator, et cetera. So perhaps

that could be cleaned up. That's a simple matter of what to do if Wire A doesn't work and laser -- I don't think that's been well delineated.

Are there any other parts of the IFU that people would like to elaborate on in terms of actual use, hands on?

DR. KRUCOFF: Warren, I guess the only question we haven't gotten to asking that was in the back of my mind is whether in general you finish a case over this wire or whether there are cases where you would withdraw or swap through the balloon or whatever.

I agree with you. I think there are probably some technical nuances that could go into instructions for --

CHAIRMAN LASKEY: Yeah, and now that I think of it, this whole issue about stents and value of adjunctive stents I think needs to be sorted out in your indications for use. If it's part and parcel of this procedure, of this strategy for patient management, then I think it needs to be clearly laid out where you recommend stenting and

where you don't.

We heard some interesting options today in real life. That just needs to make its way into the package.

DR. SOMBERG: But if it weren't -- I just need to interject something. Would you be satisfied if, let's say, it was effective as initial strategy to try to put a wire down? Twenty percent of patients you could not do it. The laser was helpful and then they went ahead and got down to a small lesion and had to put one stent in, et cetera.

That may not test all of the possibilities, and maybe you don't need the stent. Maybe you need, you know, an extra three centimeters to stent above and below that area, but you wouldn't be advocating they have to explore all of those possibilities?

CHAIRMAN LASKEY: No, no, but in the era we live in where stents rule and probably will for quite some time, I think we're being naive if we leave our head in the sand on this, that many peripheral vascular procedures will involve stents

and with some chemicals attached to them. So I think we need to just be aware of that.

This appears to be a useful adjunct, sort of standard. Perhaps together they're better, but you just need to clear that up in the instructions for use.

DR. TRACY: Warren, can I just add that if you just look at the section on directions for use without getting too hand tying to the clinician, if this was an approvable device, this is fairly generic and also fairly good at describing the technical directions for use.

So I think some of the other concerns that we have about the specifics that you're discussing may never end up in the directions for use. I think if you're just analyzing directions for use, you take it out of the pack. You put this wire down such-and-such. They look fine to me.

I don't know what the question is. If it's a question of does this look okay, I'd say the answer is yes. Is there more than could be there? Not necessarily even if we had more specific

information. So I'm not sure what exactly the FDA question is.

DR. ZUCKERMAN: Okay. Dr. Tracy, in general, I would agree with your gestalt as to how we look at contraindications, warnings, and precautions. I think what Dr. Laskey is leading you to is to Question 7, which is more directed towards what should go into the description of the clinical trial. It's on page 3 of the label, and it has some of these subset analysis that you've talked about, and maybe if you look at Question 7 it will help you determine whether some of this information should be in the clinical trials description.

CHAIRMAN LASKEY: And this is a clinical trial in which there was 98 percent use of balloons and X percent use of stents. So that's going to be hard to overlook. So I think it's part of the package.

So seven.

MS. WOOD: Please indicate if the following findings are sufficiently robust to warrant incorporation in the label:

(a) The 110 LACI patients in Rutherford Clinical Categories 5 and 6 experienced 15 percent mortality and an amputation rate of seven percent. This contrasted with one percent mortality and two percent amputation rate in 45 Category 4 patients.

(b) Seventy limbs in the LACI study also required stent placement. Stents were placed in 56 superficial femoral arteries (SFAs) in the 104 limbs with SFA lesions. Forty-nine, or 87.5 percent, of the SFAs with stents remained amputation free at six months.

DR. NICHOLAS: My response is yes. I think both should be included because 7(a) regarding the Rutherford classes and outcome bears upon case selection, and it might have a significant influence on choice of patients for whom the procedure would be recommended.

Seven (b) gives support to the comments that Warren just made about virtually everybody gets balloon angioplasty. Then the 80-some percent get a stent in their SFA if this type of procedure is expected.

So I think the operator looking at those instructions would be well served that he or she knows they are going to be moving on to balloon and/or stenting after they've utilized the laser.

CHAIRMAN LASKEY: So as statements they certainly should stand.

MS. WOOD: Okay. Are you ready to move to eight?

CHAIRMAN LASKEY: Yes.

MS. WOOD: The sponsor has proposed the following training requirements in the draft instructions for use:

"The use of the CVX-300 Excimer Laser System is restricted to physicians who are trained in atherectomy, percutaneous transluminal coronary angioplasty, PTCA, and who meet the training requirements listed below. These requirements include, but are not limited to:

"1. Training of laser safety and physics.

"2. Review of patient films of lesions that meet the indications for use.

"3. A review of cases demonstrating the CLiRpath catheters in lesions that meet the indications for use.

"4. A review of laser operation followed by a demonstration of the CVX-300 Excimer Laser System.

"5. Hands-on training with the CVX-300 Excimer Laser System and appropriate model.

"6. A fully trained Spectranetics representative will be present to assist for a minimum of the first three cases.

"7. Following the formal training session, Spectranetics will make available additional training if so requested by the physician, support personnel, the institution or Spectranetics."

Please comment on whether these training requirements are adequate.

DR. WHITE: Warren, I don't see why we're asking for coronary angioplasty as a certification for this. It should be peripheral angioplasty, not PTCA, but PTA.

And I'm not quite sure what we mean by "atherectomy," since that's generally a procedure that we don't do anymore in the leg. So I would think that the qualification for using this device would simply be someone who was angioplasty credentialed in the periphery.

CHAIRMAN LASKEY: Yes, Dr. Maisel.

DR. MAISEL: I'm not sure I see a need for Number 6, that a fully trained Spectranetics representative needs to be present. Certainly that would make sense for a physician who's not at all trained in this, but if the device were ultimately approved and a physician were trained and it's passed on from physician to physician or physician to fellow, I'm not sure that that is a necessity.

CHAIRMAN LASKEY: That's a CYA kind of thing.

DR. WHITE: Actually I think that it's important that that be there because you don't want the company to withdraw support, and for the initial -- I mean, it's certainly up to the institution. If you've been using this device in the coronaries for

three years, it's not going to be a problem to use it in the legs, but I think if you're going to use it for the first time in the legs, it's important to have, I think, someone who understands the operation of the device.

So I think that's fair enough to leave.

CHAIRMAN LASKEY: A proctor would be better, but that's an opinion.

DR. NICHOLAS: To start at the bottom, I think Number 6 should be rephrased also, three proctored cases, but I think also the first paragraph of italicized qualifications should not be there because it becomes very restrictive and, again, brings into the issue of which group of doctors is going to be able to take care of these patients. And you get access to the right tool rather than the individual skills of an individual.

DR. WHITE: Did you just say that you think a proctor needs to be there? The first part of that, did you --

DR. NICHOLAS: Well, the question of Number 6 which was raised of do you really need

somebody there to watch you do the first three if you have already been doing coronary lasers. Probably not, but if you're going to write a standard for the use of the device, supervised three times or have experience with X number of procedures at the coronary level, I think, would meet the needs.

DR. WHITE: I guess I just want to make sure that we're not overreaching a little bit because I really don't think a proctor -- it would not be a good use of my time to go watch somebody do this. I don't think this is a -- I mean, it's a skill, and there's some sense, some tactile sensation, but this is not something that an expert, a company person can't easily walk you through.

This system is, I think, actually pretty user friendly. The hardest part to me in the system is actually setting up the laser and the software, and that's what generally the company guy does better than anything else. Actually advancing catheters over guidewires, whether they're lasers or balloons or stents, are all kind of -- so I think a

proctor is probably not a great addition to that, but I think the company support is.

DR. NICHOLAS: But you'd rather see the company representative there?

DR. WHITE: I would.

DR. NICHOLAS: I have no dispute with that.

DR. KRUCOFF: Maybe another way of approaching this is do you really need to concentrate on training a physician or could you profile how to establish whether or not a site is ready, and where certification could be to have at least one physician on site who has done at least three cases and a staff who knows how to operate the device, and from there on they can train their own, you know, if they have younger people coming in.

But one way of approaching this might be in the same way we've done other technologies that have multiple pieces like this, is for the company to make sure that a site has the resources on site that it needs to know what it's doing and then after that let them do their thing.

CHAIRMAN LASKEY: Gary, to pick up on your thought, how about the use of the CVX-300 Excimer Laser System as restricted to physicians who are trained in peripheral vascular intervention? Do you to like that?

DR. NICHOLAS: No, I'd be fine with that.

CHAIRMAN LASKEY: Okay. I think we ought to get rid of the PTCA. We ought to get rid of cardiologists -- I mean in this sense --

(Laughter.)

DR. WHITE: Agreed.

CHAIRMAN LASKEY: Okay. So wording is "trained in peripheral vascular intervention." All right.

DR. ZUCKERMAN: And is there consensus on Dr. Krucoff's comments that Points 1 through 6 could be rewritten with the sponsor to certify site training as opposed to individual physician training for each physician at that site?

CHAIRMAN LASKEY: You could add that to one through six. I'm not sure it supplants it.

DR. KRUCOFF: I would supplant it. Just make it a condition of selling the catheters to a hospital and let the hospital carry it forward from there.

CHAIRMAN LASKEY: I don't have any strong feelings on that.

DR. NICHOLAS: I think it needs to define what the package is going to be that gets hospital approval, and I think one through six or seven really do that.

DR. KRUCOFF: Yeah, basically I agree, Gary. I think, you know, if you have one through six for at least one doc on site and you train the staff because, as Chris says, the interventionalist is just a point and shoot person, and apposition and I mean there are a lot of important elements to that, but the staff setting of operating the instrument is the other piece.

And after that I think you can train your own.

DR. WHITE: The one concern I would have is that in many hospitals, in ours certainly, this

device is used in multiple locations. It can be taken down to the operating room and used by a surgeon. It can be brought to the cath. lab. It can be used in radiology.

And so if you simply train a guy in the cath. lab to do this, that expertise may not travel to the operating room, and so I think that if you actually link the usability to the user, then if the surgeon wants to use it in the OR, he's going to get this education. It may be redundant for what the cath. lab has done, but it probably is not a bad thing to do.

DR. ZUCKERMAN: So what is the consensus?

DR. TRACY: I would leave it more training is better, more is better.

CHAIRMAN LASKEY: We would leave it, but add niches. I mean, that's an option.

DR. ZUCKERMAN: Okay.

CHAIRMAN LASKEY: May I take this opportunity to point out there's no patient information brochure, nothing for the patient? I

think that needs to be added to the pile.

Good. Dr. Zuckerman, does the FDA have any additional comments?

DR. ZUCKERMAN: Just one moment.

(Pause in proceedings.)

DR. ZUCKERMAN: Okay. No additional comments. Thank you.

CHAIRMAN LASKEY: Thank you.

And for the sponsor, does the company have any additional comments or questions before the vote?

DR. LAIRD: I would like to thank you for your time, and I would like to make a few additional comments.

I think obviously there were some limitations to this study design that the FDA helped us device, and they have been well, you know, ground through today.

The challenges of trying to demonstrate efficacy against a historical control where the majority of the patients did not receive an intervention, I think, is really sort of an

insurmountable problem, but I feel extremely confident that we have demonstrated safety for this device in this population of very sick people, and by any measure of historical data treating patients with critical limb ischemia, we achieved excellent results.

I think if I were to ask any of you would you accept a procedure for your patient that had zero percent, 30-day mortality and a limb salvage rate at six months of 92 or 93 percent, I think in general you would be very happy with that therapy.

And we can do randomized studies, and I can predict what that randomized study will look like. We will randomize laser assisted angioplasty against PTA, and in that study, despite our best efforts, 50 or 60 percent of the patients in each arm of the trial will get stents.

And three years from now we'll sit here and we'll try and tease out what the benefit of the stent was and how it impacted on the laser or the balloon results, and we will be nowhere and we will

have lost a lot of time, and I think our patients will have suffered because of this.

I don't personally, as a person who takes care of patients with peripheral disease every day, see any other alternatives in terms of a randomized trial. We can randomize against amputation, but I would put you in my shoes. How would you like to offer a patient the alternative of a percutaneous intervention or having a below knee amputation?

We could certainly try and randomize against surgery with a synthetic conduit in patients who don't have any lower extremity saphenous vein, but even trying to do any kind of randomized trial where you randomize against surgery is challenging at best.

I think we have done the best we could with a very difficult patient population and have demonstrated extremely good efficacy despite this challenging patient population with very low complication rates, and I think you have the opportunity here to approve a device for these

patients that can help them, and it can be labeled in a manner; say, perhaps this can be labeled as a device that in conjunction with the usual tools, balloon angioplasty, perhaps stenting, has the opportunity to provide an excellent limb salvage rate for these patients.

Thank you.

CHAIRMAN LASKEY: Thank you, Dr. Laird.

Comments from industry? Mr. Morton?

MR. MORTON: Well, I'd like to echo what we've heard all day, to just acknowledge that the presentations have been excellent. Obviously, the investigators are passionate about the benefits of this device for a very sick patient population.

I'd like to give special thanks to the Agency because earlier today they helped clarify what the requirements were for valid scientific evidence. There was a question about randomized controls, prospective controls, and as a matter of fact, those are not required by law, and I appreciate that clarification.

Today we've seen an example of the

dilemma that the FDA and the sponsor often have when they're trying to design a study, and a control may not be available. It may not be ethical in some cases, and a study is developed the best that we can with what we know at the time.

And then as that study goes on, other things happen. New medications, new techniques, new devices come out, and at the end of the day when the study is complete, you might not have designed the study that way, but nonetheless, you've done the study, and you must make use of the data that you have.

So, again, I thank the panel. I thank the Agency for that clarification, and I'd ask the panel to keep that in mind today and also in future reviews.

CHAIRMAN LASKEY: And Dr. Hughes on behalf of the consuming public.

DR. HUGHES: Thank you very much.

I also want to commend the sponsor and the FDA for their presentations, and also my colleagues here on the panel for their in depth and

insightful analysis and review, you know, of this device.

I have just one question. I hope it's okay to ask this at this point to the sponsor. Those patients, you know, who had a limb amputated, to what extent or to what degree would they be -- any of them -- be candidates for a prosthetic device? Any hope at all? Any chance at all?

I didn't quite get a sense of whether in terms of quality of life that, you know, once amputated are we talking about just having a stump and there not being any chance at all of any kind of a prosthetic device?

DR. RAMAIAH: Well, I think it all boils down to the question of amputation versus revascularization, and a lot of studies have been done. The Delphi Consensus Study is there which evaluated about 956 patients. Between radiologists, cardiologists, and surgeons, there was only a small percentage, nine to ten percent, which said that amputation should be the primary treatment.

Quality of life question is quality of

life studies have been done on patients who have been amputated, and obviously it has shown that those who revascularize or those who have options for revascularization do a lot better in terms of depression, in terms of social affability, social interaction, and in terms of physical mobility.

So revascularization is definitely the way to go in terms of amputation.

Having said that, if there is no other option of revascularization, then obviously amputation is the only treatment, and there is -- at the current rate of prosthetic development, these patients can be rehabilitated, but if you compare them to the patients who have been revascularized, obviously quality of life is definitely better for the patient with revascularization than the patient with an amputation that is being rehabilitated.

DR. HUGHES: Okay. Thank you. I think I understand, you know, what you're saying there.

And also, I guess, trying to get a really clear sense of alternatives, I believe it is outlined rather well in Section 2, the summary of

safety and effectiveness, somewhere around, I believe, page 26, but I really want to get a clear sense.

This particular device and procedure, this LACI, it would be pretty much considered last resort, wouldn't it, or would it not? Last resort?

DR. LAIRD: Well, I think the standard of care in most places for patients with this problem is surgical revascularization, and the study design was basically looking at a group of patients who, in essence, had very, very few options. They were not good candidates for surgery, and they had very diffuse disease, and they had critical limb ischemia. So they were at great risk for losing their limb.

So, in essence, yeah, it's sort of a last resort, you know, last stop before potentially going on to amputation.

DR. HUGHES: Okay. Thank you.

Okay. Those are just a couple of things I really wanted to get clear in my mind in terms of a consumer representative.

Once again, I think that the panel has, you know, done its job very, very well in ferreting out, you know, these issues, very complex issues in terms of comparing the population for the LACI procedure to those in the control group and that not being really appropriate is the way that I see it.

But I think that the panel in the end most likely will have some very good recommendations, you know, concerning that kind of issue. I think they're coming out already.

So anyway, I just want to leave it at that. I think everyone has done as best a job as conceivable and reasonable under the circumstances.

Thank you.

CHAIRMAN LASKEY: Thank you.

I'd like to just briefly open the open public hearing portion again. Is there anyone who wishes to step forward and address the panel on today's topic?

(No response.)

CHAIRMAN LASKEY: If not, I'll close the open public hearing portion and ask Ms. Wood to read

the voting options.

MS. WOOD: The Medical Device Amendments to the Federal Food, Drug and Cosmetics Act, the Act as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device pre-market approval applications, PMAs, that are filed with the Agency.

The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

Safety is defined in the act as a reasonable assurance, based on valid scientific evidence, that the probable benefits to health under the conditions of intended use outweigh any probable risks.

Effectiveness is defined as a reasonable assurance that in a significant portion of the population the use of the device for its intended uses and conditions of use when labeled will provide clinically significant results.

Your recommendation options for the vote are as follows:

Approval if there are no conditions attached;

Approvable with condition. The panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes, or a further analysis of existing data. Prior to voting, all of the conditions should be discussed by the panel;

Not approvable. The panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe or if a reasonable assurance has not been given, that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Following the vote, the Chair will ask each panel member to present a brief statement outlining the reason for their vote.

CHAIRMAN LASKEY: Thanks, Geretta.

So the recommendation of the panel may

be approval, approvable with conditions that are to be met by the applicant, or denial of approval.

I will now ask for a motion on the PMA.

DR. NICHOLAS: I would move that the proposal not receive approval based on the fact it has not been shown to be effective, but certainly, I think, has shown to be safe.

DR. SOMBERG: I second the motion.

CHAIRMAN LASKEY: Is there a second?

DR. SOMBERG: Second.

CHAIRMAN LASKEY: So it has been moved and seconded that the PMA is denied approval.

DR. ZUCKERMAN: Now the panel needs to vote on that motion.

CHAIRMAN LASKEY: Okay. So can we engender, at risk of prolonging this discussion of this motion? If not, I suggest we vote on the motion.

Again, the motion is to deny approval. All in favor of denying the approval, raise hands, please. High.

(Show of hands.)

CHAIRMAN LASKEY: We're counting right? So one, two, three, four, five, six, seven, eight, nine in favor of the denial of approval.

All against?

(Show of hands.)

CHAIRMAN LASKEY: One.

DR. ZUCKERMAN: For the record, Dr. Laskey, can you indicate who voted for and against?

CHAIRMAN LASKEY: Yes, I can. Voting for were Drs. Nicholas, Tracy, Maisel, White, Ferguson, Morrison, Somberg, Krucoff, and Normand.

And voting against was Dr. Aziz.

So shall we just finish up with each person's short rendition of why? You stated your position very well, Gary.

DR. NICHOLAS: Well, I think that there's been a strong argument made by the investigators that there's a role for this excimer laser possibly in that short lesion propagated with clot proximal to it. I think Dr. Gray presented that very well.

There's clearly a nidus here for

providing information that will allow us to approve this technology, and I'd encourage the investigators to design the study that will allow us to do that.

DR. TRACY: I also voted for not approvable, and I just echo the opinion that effort needs to be put into finding a control group that's suitable, and that may not in my mind require additional investigation, a new clinical study, but may require identification of some better control group from the literature.

DR. MAISEL: I voted for not approvable for all of the reasons we have discussed previously and agree that I'm quite comfortable with the safety data that's been presented, and it's been an issue of effectiveness and appropriate control group comparison.

DR. WHITE: I voted for not approvable based upon my conviction that there needs to be, I think, a contemporaneous control group so that we can tease out, I think, the adjunctive benefit gained from the laser. I think that there may be an option to look at a group of patients who are not

candidates for intervention, and that's certainly -- particularly given the 13 percent or 14 percent of patients who are not treatable with a guidewire crossability, but I don't think there's enough data in this PMA to support that as an exception.

DR. FERGUSON: I voted for not approvable for the reasons that have been given around the table, with considerable angst, I might say, because in my heart I feel that this is a viable option, and it's a good option, and I think I agree with Dr. Tracy. I think that there are ways to salvage this by appropriate multi-institutional studies or some other way without going through a very large study again as you've done this time.

DR. MORRISON: Well, I also voted for not approvable with considerable reluctance because I think this is a very sick group, and I think demonstration that there are even a small cohort where the adjunctive use of laser would allow a successful procedure really could be adequate, but unfortunately I don't see the current control group as providing that evidence.

So with some reluctance, I voted for not approvable.

DR. SOMBERG: I also voted for not approvable for essentially the reasons that have been mentioned by fellow panelists. I am very concerned that this could discourage the development of catheter sizes that are necessary for peripheral vascular, and I do think there's benefit here, and I think it may be culled from the current data set or from additional data sets.

And I also would like to underscore what I was trying and I think other people have mentioned as well, that there are other things between mortality and more drastic endpoints like amputation and not, such as quality of life, healing, et cetera, which could be compared if a new days is set or was necessary that would not take as long as or be as arduous as this particular study.

But lacking evidence and proof that there is efficacy, it would be a gross violation of our mission to approve.

DR. KRUCOFF: I also voted for not

approvable for many of the same fundamental -- I think this is a data set that clearly illustrates safety in a highly frail population. I can echo the reluctance of saying no to the obvious impression of the individuals who have used this device in these patients that it may well have an important adjunctive role, and that this may set back the time line of our ability to reach those patients.

I do think on the efficacy side that I would really encourage the sponsor and the investigators to think about short, doable ways. You know, John, I feel the spirit of the randomization issue, but it's very different if you approach somebody and say, "I've got a trial that's 50-50, 50 percent chance we're going to cut off your leg, 50 percent chance we'll use a laser."

That's a different conversation than going to a patient who's imminently going to have their leg removed and saying, "We have a trial that at least would have a 50-50 chance of trying something different."

And I do think randomization in some of

these patients is feasible, and in a randomized cohort what I would urge you to do is think about a technical endpoint that would show efficacy at a technical level in patients in whom routine intervention techniques are unlikely to work without laser adjunct, and to prose that in addition to this safety data you've already collected, I would personally find that a very favorable way to try and briskly with a modest randomized trial bring this device forward.

Another suggestion in the really, really, really sick patients who have bad anatomy and multiple co-morbidities, to consider and even dialogue around whether a human device exemption, an HDE path, a non-randomized path might be something that could be discussed in really the ultra sick where there are truly no other options, and see if those patients could be identified.

So I really hope that some additional data would be enough to help us all understand data supporting efficacy in addition to all of the hard work that has been done that has provided, I think,

key data on safety.

DR. AZIZ: I voted that it should be approved. I agree that the trial design was not perfect. I think it did demonstrate that it was safe. I think the efficacy, I think, in this trial under this device and in other devices where you have ongoing concurrent, other therapies like angioplasty and stents is going to confuse the patent both with this device and in the future.

And I think I don't know quite how to answer that sort of dilemma, and even though the effectiveness was not pure, I think there are a group of patients who really are -- who have the only option is that of amputation. So I hope that even though that this is obviously not going to pass down, that there would be an exemption or a compassionate use because I think as the data here showed in some of the cases, those legs were truly saved.

DR. NORMAND: I voted not approvable basically for the reasons that were mentioned earlier, but I want to emphasize I'm not necessarily

advocating use of a randomized trial. My concerns were related to what I believe to be a poor analysis of observational data, and I think there's a good way to go forward with registry data.

You unfortunately didn't have the covariate information, but I think there's reasonable and surely sound statistical methods to help go forward without a randomized trial to adjust appropriately for differences.

CHAIRMAN LASKEY: Well, we are clinicians up here, and I just want to applaud the sponsor and applaud Dr. Laird for really a cogent presentation. I think we're all sensitive to how dire these patients are. This is almost destination therapy, if you will, and perhaps some clever configuring of the adjunctive/conjunctive aspect of this device will go a lot further than is apparent right now.

But again, I'd like to thank the sponsor, again, Dr. Laird and my panel members.

This concludes the report --

DR. ZUCKERMAN: Dr. Laskey, before we

conclude, can we just comment on several options made by panel members here?

There have been two potential ways to move forward. Dr. White and Dr. Somberg have developed the idea of perhaps another trial where this is looked at as more of a niche device for patients where guidewire crossing is not possible.

Our general experience with that type of trial design has been somewhat problematic in defining when a guidewire can cross a lesion, and you should try a different modality.

Could you give any other helpful hints, Chris?

DR. WHITE: Well, I think I've participated in trials that required guidewire failure, and I think that, I mean, those trials aren't dependent upon the integrity of the investigator. I mean, you have to trust somebody sometime, and while I understand that you could possibly subvert the intention of the trial, I still think if you make the argument that 15 percent of these patients or 13 percent of these patients were

not treatable had the laser not been available, then that well could be an indication for this device in the periphery.

And so I think that is worth pursuing for that reason. I don't know how to make people more honest or I don't know how to quantify water failure. I'm not trying to make a laser pass, and I don't know how to -- you know, the guidewire police can only visit so many institutions. So I think you just have to trust the integrity of the investigator.

DR. SOMBERG: Just very quickly, I would inject, Dr. Zuckerman, that it's one thing to do a trial only like that and present you the data, but in this particular case there is all of this other data, and there is a trend to feel, from what I'm understanding from most of the panel, that there may be some benefit here, but the problem is there was no way to show that scientifically.

So, therefore, if you're going to say, well, this is going to be an adjunctive device and you have a choice of no data or having a feeling

that something may work, but now all of a sudden you have demonstration that it's a technical tool, it might be useful.

Also, the way to get around the guidewire police is not to randomize everybody, but obviously to have the population get some other therapy or the procedure is stopped and then some people get the laser therapy. So that would be able to allow for the fact that sometimes somebody might have been able to squeeze a guidewire through or something like that to see if it really opens that lesion up.

But I mean, there are ways of getting around it, but I think the point people were trying to convey is that there's a lot of information here. Unfortunately, it's not one that could be codified in a statistically significant package. There may be a technical tool package might be useful to bring this rapidly to the fore.

DR. ZUCKERMAN: Fine, and then one final question for Dr. Krucoff, who suggested in a subsequent randomized trial a technical endpoint

rather than the endpoint used here could be utilized. Do you have some suggestions for that technical endpoint?

DR. KRUCOFF: I actually think they're related because it would be a reach, cross, and dilate in a cohort of patients who could be selected for a likelihood that you're going to start doing some of those or actually in this data set, and then how you handle the interventionalist bias, I think, again, one way to do it is to say in patients who you can't reach, cross, and dilate, although you tried to randomize them or to just count on the integrity of your selected investigators and randomize them ahead of time so that if you are unable to reach, cross, and dilate without adjunctive laser, could you then apply the laser and come to a different end?

And I guess what that would beg would be necessarily the six-month follow-up and which actually could be treated more in a modular way as safety elements that could be reported later for completeness, but allow a decision about bringing

the device to market to be earlier perhaps with an earlier 30-day or even indexed hospitalization primary endpoint of efficacy, given what you already have in hand about safety.

If that was something the Agency would consider, that would at least accelerate the time line that would be required to gather a sufficient cohort of patients to bring the question of the effectiveness of this adjunctive use back to the table.

CHAIRMAN LASKEY: I would like to suggest to the Agency that they go beyond six months. I think that's an overly optimistic point at which to truncate the observation. I think that there's enough events out there which are cumulative that I don't think we have a real picture of what the success is.

So this concludes the report and recommendations of the panel on PMA P910001 from Spectranetics Corporation for a CVX-300 Excimer Laser System for the treatment of patients with critical limb ischemia.

Again, thank you all.

(Whereupon, at 3:31 p.m., the meeting was concluded.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Circulatory System Devices Panel

Before: DHHS/PHS/FDA/CDRH

Date: October 2, 2003

Place: Gaithersburg, MD

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.